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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Paper No. 19

Serial Number: 08/446200
Filing Date: 5/19/95
Appellant(s): Freeman et al.

Date mailed 7.19.99

Jane Remillard
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's Brief on Appeal filed 5/7/99 (Paper No. 18).

The text of those sections of Title 35 U.S.Code not included in this appeal can be found in a previous Office action herein.

(1) Real Party of Interest.

A statement identifying the real party of interest is contained in the Brief.

(2) Related Appeals and Interferences Identified.

A statement identifying that no related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the Brief.

(3) Status of Claims.

The statement of the status of claims contained in the Brief is incorrect.

This Appeal involves claims 1-4.

(4) Status of Amendments After Final.

The appellant's statement of the status of amendments after final rejection contained in the Brief is correct.

(3) **Summary of Invention.**

The summary of invention contained in the Brief is correct.

(4) **Issues.**

The appellant's statement of the issues in the Brief is correct.

(5) **Grouping of Claims.**

The appellant's statement in the Brief that certain claims do not stand or fall together for the reasons set forth below in the Brief is not agreed with because such reasons are not readily apparent from appellant's arguments, nor for the reasons of record.

(6) **Claims Appealed.**

The copy of the appealed claims contained in the Appendix to the Brief is correct.

(7) **Prior Art of Record.**

The following is a listing of the prior art of record relied upon in the rejection of claims under Appeal.

A) Hathcock et al., J. Exp. Med. 180: 631-640 (1994).
B) Linsley et al., U.S. Patent No. 5,580,756.
C) Kuchroo et al. Cell 80: 707-718 (1995).
D) Janeway et al. Cell 76: 275-285 (1994).

(8) **Grounds of Rejection.**

The following ground(s) of rejection are applicable to the appealed claims.

Rejection Under 35 U.S.C. § 103

Claims 1-4 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hathcock et al. (J. Exp. Med.,1994) in view of Linsley et al. (U.S. Patent No. 5,580,756), Kuchroo et al. (Cell, 1995) and Janeway et al. (Cell, 1994).

Hathcock et al. teach the expression, regulation and function of B7-2 and that B7-1 and B7-2 are expressed/induced with differing kinetics and play different roles in initiating and maintaining an immune response (see entire document. For example, Hathcock et al. teach that in response to LPS or anti-IgD-dextran, murine B cells express B7-2 earlier and at higher levels than B7-1 and that such quantitative differences in the amount of B7-1 and B7-2 expressed on activated B cells may profoundly influence their contribution to costimulatory function (Pages 634 and 638, in particular). Hathcock et al. do not teach using immobilized B7-2 to stimulate activated T cells and induce their differentiation into Th2 cells.

Linsley et al. teach using soluble B7 including fragments and derivatives to stimulate T cells (see entire document). Linsley et al. teach that B7 antigen is reacted with T cells in vitro to crosslink or aggregate the CD28 receptor, for example, using CHO cells expressing B7 antigen or immobilizing B7 on a solid substrate, to produce activated T cells (see column 12, lines 14-17, in particular). Linsley et al. teach that T cells are activated with anti-CD3 and the further stimulated with either a stimulating anti-CD28 antibody or soluble B7-Ig fusion protein. Immobilized soluble B7 enhances proliferation of activated T cells (see column 32 and Table 2, in particular). Linsley et al. do not teach that activation of T cells using immobilized soluble B7-2 induces Th cells to differentiate to Th2 cells.

However, Kuchroo et al. teach that their data in experiments using anti-B7-1 and anti-B7-2 antibodies are direct evidence that interaction of the costimulatory molecules B7-1 or B7-2 with their counterreceptors CD28 and CTLA-4 on T helper precursors (Thp) during antigen presentation leads to polarization of Th responses and that the simplest interpretation of their data is that B7-1 preferentially acts as a costimulator for the generation of Th1 cells while B7-2 costimulates and induces Th2 cells (see entire document, particularly page 715, column 1 and Figure 7). Kuchroo et al. teach that the identification of intracellular signals that are generated by interaction of B7-1 and B7-2 with the same counterreceptors (CD28 and CTLA-4) on a Thp cell may provide insight into the molecular mechanisms responsible for Th cell differentiation, allowing selective manipulation of the immune response in disease (see page 715, last paragraph, in particular).

Janeway et al. teach that one of the most crucial events in the differentiation of naive CD4 T cells that respond to ligand presented together with costimulators is the decision whether to become a helper CD4 T cell (Th2), specialized for the activation of B cells to secrete antibody, or an inflammatory CD4 T cell (Th1), specialized to activate macrophages and stimulate cell-mediated immunity (see page 281, column 2, in particular). Janeway et al. teach that if the biochemical nature of differential signaling pathways are known, pharmacological agents can be developed capable of diverting T cell responses from harmful to innocuous by getting the T cell to reinterpret the signals it is receiving via its receptors.

Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to stimulate CD3-activated T cells to differentiate to Th2 cells by activating them with immobilized soluble B7-2. One would have been motivated to substitute soluble B7-2 for B7 in the teachings of Linsley et al. because of Hathcock's teaching of B7-2 on activated B cells, Kuchroo's teaching that interaction with B7-2 induced activated T cells to differentiate to become Th2 cells, and Linsley's teaching that immobilized soluble B7 was very effective. One would have been motivated to combine these teachings because signals involved in Th cell differentiation was a problem important in the art as evidenced by the teachings of Kuchroo et al. and Janeway et al., for example. Based on the teachings of Linsley et al. and Kuchroo et al., for example, one of ordinary skill in the art would have a reasonable expectation of success in modulating the immune response by immobilized, soluble, stimulatory B7-2. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

(10) Response to Argument

Rejection Under 35 U.S.C. § 103

Appellant's arguments, filed 5/7/99 (Paper No. 18), have been fully considered but are not found convincing essentially for the reasons of record.

Appellant argues that the cited references alone or together fail to teach or suggests the claimed methods.

Appellant argues that the references do need to be argued to decipher the teachings of the references.

Appellant reviews the Summary on page 631 of Hathcock et al., but argues that Hathcock et al. Do not teach nor suggest modulating a Th2-type response by contacting the cells with an agent which modulates a B7-2 induced signal. Appellant further argues that there is no teaching of a differential role of B7-1/B7-2 in Th1/Th2 responses. Appellant relies upon the observation that the kinetics of peak expression of the two costimulatory molecules B7-1/B7-2 were not different on page 638 of Hathcock et al. and the comments that it was not known that B7-1/B7-2 mediate distinct or overlapping costimulatory functions. Appellant asserts that there was not motivation for making the claimed invention.

However in contrast to appellant's assertions and as pointed out above and of record; Hathcock et al. clearly teach the expression, regulation and function of B7-2 and that B7-1 and B7-2 are expressed/induced with differing kinetics and play different roles in initiating and maintaining an immune response (see entire document, including the Abstract and Discussion). Hathcock et al. differs from the claimed methods by not teach using immobilized B7-2 to stimulate activated T cells and induce their differentiation into Th2 cells.

Appellant argues that Linsley et al. Does not make up for the deficiencies of Hathcock et al. Because Linsley et al. Fails to distinguish between the B7-1/B7-2 molecules and fails to motivate the ordinary artisan to modulate Th2-type response by modulating B7-2.

However in contrast to appellant's assertions and as pointed out above and of record; Linsley et al. teach the art known application of crosslinking costimulatory molecules such as immobilized soluble B7 molecules along with T cell activation signals such as anti-CD3 antibodies to produce activated T cells (see column 12, lines 14-17; column 32 and Table 2 for example). Linsley et al. Would not have taught B7-2, because B7-2 was not discovered until 1993, after the priority date of this reference. However, Linsley et al. clearly teaches teach the use of immobilized soluble B7 molecules to stimulate T cells of interest at the time the invention was made.

Appellant acknowledges on page 8 paragraph 2 of the Brief that Kuchroo et al. Teach that CD4 helper T cells mature along two alternative pathways (Th1/Th2) and that these two pathways are differentially activated by B7-1/B7-2. However, appellant argues that Kuchroo et al. Fails to teach or suggest contacting these cells with an agent which modulates a B7-2 signal. Appellant's arguments concerning modulating cytokine production with anti-B7-2 antibody does not detract from the clear teaching by this reference and acknowledged by appellant that Kuchroo et al. Clearly teaches the differential maturation of T cells to either Th1/Th2 via B7-1/B7-2 signaling (see entire document, particularly pages 714-715, Roles of the Costimulatory Molecules B7-1 and B7-2 in Th Cell Differentiation).

Page 715, column 1, lines 9-12, state that the "The simplest interpretation of our data is that B7-1 preferentially acts as a costimulator for the generation of Th1 cells while B7-2 costimulates and induces Th2 cells (see model in Figure 7)". Page 715, column 1, lines 15-19, state that "If this hypothesis is correct, then the interaction of B7-1 and B7-2 molecules withe their T cell counterreceptors likely generates different intracellular signals that lead to the differentiation of Thp cells along a Th1 or Th2 pathway".

In contrast to appellant's assertions, Kuchroo et al. clearly provides strong motivation and expectation of success of selectively modulating a Th2-type response with a stimulatory form of B7-2.

Appellant argues that Janeway et al. does not make up for the deficiencies of the other references because this reference doe snot teach or suggest agents which modulate a B7-2 signal.

However, as appellant acknowledges; Janeway et al. Provide for describing adaptive immune into either Th1 or Th2 cells. As pointed out above and of record, Janeway et al. provides further motivation at the time the invention was made to discern and characterize the nature of Th1/Th2 differentiation and, in turn, to apply this knowledge to pharmacological manipulation.

Appellant argues that the both the suggestion and the reasonable expectation of success must be found in the prior art and not in applicant's disclosure. Appellant's reliance on In re Dow Chemical Co. 5 USPQ2d 1529 (Fed. Cir. 1988), Arkie Lures v. Larew Tackle 119 F.3d 953 (Fed. Cir 1977) and In re Vaeck 947 F.2d 488 (*Fed. Cir 1991), In re O'Farrell 7 USPQ2d 1673 (Fed.Cir. 1988) are acknowledged. However these citations and arguments are not found convincing in view of the clear motivation and expectation of success in the combined teachings of the prior art

Again, in response to appellant's arguments here and of record that there was no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the prior art teachings provide clear teachings and motivation for the ordinary artisan to selectively modulate Th2-type responses by activating $CD4^+$ T cells with a stimulatory form of B7-2, including B7-2 attached to a solid phase support with an expectation of success at the time the invention was made.

Appellant's arguments are not found persuasive.

(11) For the above reasons, it is believed that the rejections should be sustained.

Respectively submitted,

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